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PATENT
Attorney Docket No. 07164.0008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Susan L. WESTON et al.	)	
Serial No.: 09/228,639	)	Group Art Unit: 1655
Filed: January 12, 1999	)	Examiner: J. ENEWOLD
For: SEQUENCES	)	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE TO OFFICE ACTION

This document is filed in response to the Office Action (Paper No. 10) mailed June 14, 2000. Applicants note that the Examiner has renumbered claims 11-15 as claims 12-16. Applicants refer in this Response to the claims as renumbered by the Examiner.

IN THE SPECIFICATION:

On page 4, line 12 replace "diagnostics primer" with -- diagnostic primers --.

IN THE CLAIMS:

Please cancel claims 10 and 11 without prejudice or disclaimer, and add new claims 17 and 18 as follows:

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--17. A diagnostic kit for detecting the presence or absence of twelve mutations in the cystic fibrosis transmembrane conductor regulator (CFTR) gene which comprises sets of primers as claimed in any one of claims 1, 2, 3, 5, 12, 13, 14, or 15.

18. A diagnostic kit as claimed in claim 17, further comprising one or more of the following primers:

GAGCACAGTACGAAAAACCACCT (Seq. ID. No. 1)
AAACTTTTACAGGGATGGAGAACG (Seq. ID. No. 2)
AGAGGATTATCTATGCAAATCCTTGTAACC (Seq. ID. No. 3
TCAACTTCACTATCAAAAGTCATCATCTAG (Seq. ID. No. 4).--

Please amend the following claims:

1. (Amended) A method for detecting the presence or absence of twelve mutations in the cystic fibrosis transmembrane conductor regulator (CFTR) gene, which method comprises contacting sample genomic DNA from an individual in two separate reaction vessels with primer sets, wherein:

A) genomic DNA in the first reaction vessel is contacted with allele specific primer sets for [(A)] the 1717-1G>A, G542X, W1282X, N1303K, ΔF508(M), 3849+10kb C>T mutations, and

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B) genomic DNA in the second reaction vessel is contacted with allele specific primer sets for [(B)] the 621+1 G>T, R553X, G551D, R117H, R1162X and R334W mutations[respectively],

in the presence of appropriate nucleotide triphosphates and an agent for polymerisation, such that each diagnostic primer is extended only when the relevant mutation is present in the sample; and detecting the presence or absence of CFTR gene alleles by reference to the presence or absence of diagnostic primer extension product(s).

In claim 3, line 1 after "gene" add -- mutations --; in line 2 delete "mutations".

In claim 5, line 1 after "gene" add -- mutations --; in line 2 delete "mutations".

12. (Amended) The set of primers as claimed in claim 3 [and comprising the following diagnostic primer sequences] wherein the primers comprise the following sequences:

TCTTGGGATTCAATAACTTTGCAACAGTCA (Seq. ID. No. 5)
TACTAAAAGT GACTCTCTAA TTTTCTATTT TTGGTAATTA (Seq. ID. No. 7)
AGTTTGCAGA GAAAGACAAT ATAGTTCTCT (Seq. ID. No. 8)
TGATCACTCC ACTGTTCATA GGGATCCATC (Seq. ID. No. 10)
GTATCTATAT TCATCATAGG AAACACCATT (Seq. ID. No. 12)
ACATTTCCTT TCAGGGTGTC TGACTAA (Seq. ID. No. 14).

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13. (Amended) A set of primers as claimed in claim 5 [and comprising the following diagnostic primer sequences] , wherein the primers comprise the following sequences:

GTATCTATAT TCATCATAGG AAACACCACA (Seq. ID. No. 16)
TGCCATGGGG CCTGTGCAAG GAAGTATTGA (Seq. ID. No. 18)
AGCCTATGCC TAGATAAATC GCGATAGACT (Seq. ID. No. 19)
CCTATGCACT AATCAAAGGA ATCATCCTGT (Seq. ID. No. 21)
GCTAAAGAAA TTCTTGCTCG TTGTT (Seq. ID. No. 23)
GACTGACTGA CTGACTGACT CTGACTGACT TATTCA [(Seq. ID No. 24)]
CCTTGCTAAA GAAATTCTTG CTGA (Seq. ID. No. 24)
TATTTTTATT TCAGATGCGA TCTGTGAGTT (Seq. ID. No. 26).

In claim 15, line 12, after "TATTCA" remove "(Seq. ID. No. 24)".

16. (Amended) A set of primers as claimed in any [of claims 1-8] one of claims 1,2, 3, 5, 12, 13, or 14, and comprising one or more of the following control primers:

GAGCACAGTA CGAAAAACCA CCT (Seq. ID. No. 1)
AAACTTTTAC AGGGATGGAG AACG (Seq. ID. No. 2)
AGAGGATTAT CTATGCAAAT CCTTGTAACC (Seq. ID. No. 3)
TCAACTTCAC TATCAAAAGT CATCATCTAG (Seq. ID. No. 4).

REMARKS

Specification Amendment

Applicants have amended the specification to correct a grammatical error.

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Claim Numbering and Dependency

Applicants acknowledge the incorrect numbering of new claims 11-15 in an Amendment filed May 8, 2000. The numbering did not reflect the addition of claim 11 in the Amendment filed January 12, 1999. Thus, the claims added in the Amendment of May 8, 2000 have been renumbered as claims 12-16. Claims 1, 2, 3, 5, and 12-18 are pending in the instant application.

Claim 10 was dependent on claims 1-8. In the Amendment filed May 8, 2000, Applicants cancelled claims 4 and 6-8 and added new claims 11-14 (now correctly renumbered as claims 12-15). In order to maintain the appropriate claim dependency in light of these amendments, Applicants have canceled claim 10 and added new claim 17. Claim 11 was cancelled and added as new claim 18 and it now depends from claim 17. Claim 16 was also amended to correct dependency.

Correction to Reflect Sequence Rules

The Examiner suggested that the nucleotides listed in claim 11 are subject to U.S.P.T.O. sequence rules since they are longer than 10 nucleotides in length. The sequences must be identified by sequence identification numbers (Office Action page 2, item 3). Claim 11 has been cancelled and corresponding new claim 17 identifies sequences as Seq. ID. Nos. 1-4, in compliance with the sequence rules.

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Objections to the Drawings

Applicants acknowledge an Interview Summary sheet of September 5, 2000, in which the Examiner indicated that the drawings were approved by the draftsman.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 1-2, 10-13, and 15-16 under 35 U.S.C. § 112, second paragraph as indefinite and failing to particularly point out and distinctly claim the subject matter (Office Action, pages 3-4, item 5).

The Examiner rejected claim 1 and dependent claims 2, 10-11, and 16, arguing that it is unclear whether the two separate reaction vessels containing sample genomic DNA from a patient are contacted with both primer sets of A and B, or whether one portion is contacted with primer set A and the other portion is contacted with primer set B. Claim 1 has been amended to overcome the rejection to clarify that one vessel is contacted with primer set A and the other vessel is contacted with primer set B.

The Examiner rejected claims 13 and 15 as being indefinite because two sequences appeared to have the same Seq. ID No. This sequence is long and takes up two lines of text. Accordingly, Applicants have removed "(Seq. ID No. 24)" from the end of the first line of the sequences in claims 13 and 15, thereby overcoming this rejection.

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Claim 2 (and dependent claim 16) were rejected because of an alleged failure to distinguish between the diagnostic primers and the amplification primers. The difference between the diagnostic and amplification primers is taught in the specification. For example, a diagnostic primer is extended only when the relevant mutation is present in the sample (page 2) whereas an amplification primer does not have this qualification. Further, as described on page 4, sets of diagnostic primers can be used "in combination with further amplification primers". Pairs of diagnostic and corresponding amplification primers are provided in the tables on page 5. A diagnostic and an amplification primer are the forward and reverse primers (or vice versa) corresponding to a given mutation. Amplification primers make up a clearly defined population of primers distinct from the diagnostic primers. Therefore, the rejection should be withdrawn.

The Examiner also contends that claims 3, 5, 12, 13, and 16 are indefinite due to the language "a set of allele specific primers" in claims 3 and 5 and "diagnostic primer sequences" in claims 12 and 13. The Examiner also asserts that claims 12 and 13 do not limit claims 3 and 5 because it is purportedly unclear what the differences are between the allele specific and diagnostic primers. Applicants have removed the term "diagnostic primer sequences" in claims 12 and 13 and further amended claims 3 and 5 to overcome the rejections.

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Rejection Under 35 U.S.C. § 103

The Examiner rejected Claims 1-3, 5, and 10-16 under 35 U.S.C. § 103 for allegedly being unpatentable over Little et al. (EPO 497527A1, August 5, 1992, hereafter Little) and Ferrie et al. (Am. J. Human Genetic, Vol. 51, p. 251-262, 1992, hereafter Ferrie) in view of Estivill et al. (Human Mutation, Vol. 10, p. 135-154, 1997, hereafter Estivill) and the Cystic Fibrosis Genetic Analysis Consortium (Human Mutation, Vol. 4 p. 167-177, 1994, hereafter CFGAC) (Office Action item 6, pages 4-9).

The Examiner contends that Little teaches that the ARMS method can be used to selectively amplify multiple sites and may be useful for screening a single sample for multiple nucleotide variations. The Examiner further contends that Little also teaches that primers for the cystic fibrosis gene can be used. Ferrie teaches the development of an ARMS test for common mutations of the CTFR gene. The Examiner admits that neither Little nor Ferrie teach the specific combination of primers taught by the instant invention, and turns to the Estivill and CGFAC references, stating that the mutations underlying these primers are revealed therein. The Examiner claims that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the teachings of Little and Ferrie in view of Estivill and CGFAC to arrive at the instant invention.

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However, as part of the requirement for showing a *prima facie* case of obviousness, the Examiner must show that there is a motivation to combine the Little, Ferrie, Estivill, and CFGAC references:

> "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." (M.P.E.P. § 2142)

The mere fact that references can be modified does not render the resulting combination obvious unless the art also suggests the desirability of the combination, as taught in the M.P.E.P. § 2143.01, citing *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990).

The Examiner provided no evidence that it would have been desirable for one of ordinary skill in the art to combine the references. Indeed, the motivation and desirability to make the claimed invention are found only in the instant specification and the Examiner has not met her burden establishing a *prima facie* case of obviousness. Indeed, Ferrie teaches away from a test which uses more than the four primer sets in his invention. For example, Ferrie states that while:

> "it is often desirable to analyze samples for as many CF mutations as possible, there are practical limits to the number which can routinely be performed." (page 252)

By comparison, Applicants' teachings include 6 sets of primers per vessel for detecting a total of twelve CF mutations.

Additionally, multiplexing primers for use in a single reaction vessel is not a routine task. While multiplex tests are sometimes desirable, there is no guarantee that

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certain combinations of mutations are amenable to this approach. Thus, it would not be obvious for one to arrive at the claimed invention.

Ferrie addressed the difficulty of multiplexing primers directed to just four mutations:

> "With single tests our primary concern was with the specificity of the ARMS reaction, but with the multiplex tests, there was the added complication that the relative yields of the ARMS reactions had to be similar. Initially, the primer sequences selected for the single ARMS tests were combined into multiplex reactions. This approach did not work, because the yields of several of the reactions were too low...compared with the yield of the other reactions." (page 260)

Furthermore, Ferrie found that some primers which worked fine in single tests failed to yield a detectable product when used in a multiplex reaction. He also explained that different sets of primers can often bind to regions of the gene that are in close proximity, which can cause problems when the primers sets are used together in the same reaction (at 260).

Ferrie stated that the challenges associated with multiplexing are magnified when PCR is used:

> "In a multiplex, however, there are several competing reactions. If the efficiencies of these reactions are not similar, then each round of the PCR process will amplify the differences in the yields, leading to an imbalance in the system." (page 260)

To make the system work with PCR, Ferrie had to modify the sequences and concentrations of the primer sets to reach a precise balance (see Id.).

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In the instant invention, multiplex reactions comprising more than four sets of primers are taught by the Applicants. With each additional set of primers, the complexity of the interactions between the primers increases substantially, as does the difficulty in achieving a successful system. Applicants address the careful experimentation required to arrive at the claimed invention:

> "In designing the primers it was important to ensure that a false result could not arise due to other DNA variations at the same site or in the vicinity of the mutations....This discrimination was achieved after particular consideration and the appropriate choice of orientation of each primer....Careful attention was also given to the inclusion of additional base-pair mismatches between each primer and the genomic DNA sequence and also the length and concentration of each primer. In combining primers for multiplex analysis...it was necessary to minimize any primer interactions that might affect test performance." (page 9)

Further, the knowledge of a template sequence does not render the design of appropriate diagnostic primers obvious. Additionally, the instant invention teaches the design and use of sets of diagnostic primers, not the design and use of primers for individual mutation tests.

In summary, one skilled in the art would not have been able to provide a robust, two vessel test based on the art cited by the Examiner. Thus, Applicants overcome the rejection.

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Conclusion

It is respectfully submitted that upon entry of these amendments, this Application is now in condition for allowance. Please charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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By: _____
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Dated: September 14, 2000

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